REMARKS

Prior to this Amendment, claims 1-64 were pending. By this Amendment, new claims 65-83 have been added. Therefore, following entry of this Amendment, claims 1-83 will be pending.

Claims 1, 8-22, 27-31, 38-41, 47, 48, 53-59, and 61-64 have been amended.

Claims 1, 31 and 48 have been amended to recite a "membrane" rather than a "biological barrier." Support for this amendment is found in the specification at page 5, line 5.

Claim 8 has been amended to add a period.

Claims 12-16, 20, 21, 38-40, 57-59, 61 and 62 have been amended to make explicit that the molecular weight unit is daltons.

Claim 17 has been amended to correct a grammatical error.

Claims 30 and 56 have been amended to recite SEQ ID NOs.

Claims 1, 9-11, 18, 19, 22, 27-29, 41, 46-48, have been amended for consistency with the recitation of two or more polycationic polymers linked to the hydrophilic polymer backbone. Support for this amendment is found at page 4, line 25-page 5, line 1 of the specification.

New claims 65-83 are supported in the specification as filed. Support for new claim 65 is found at Examples 1-10, pages 18-24. New claims 66-83 are dependent claims that recite the same limitations as dependent claims 2-19.

Claim objections

Claim 17 was objected to because the second instance of "is" should be "are."

Claim 17 has been amended so that the second instance of "is" is now "are."

Claims 30 and 56 were objected to because of the lack of recitation of SEQ ID NOs.

Claims 30 and 56 have been amended to recite SEQ ID NOs as suggested in the Office Action.

Claim 48 was objected to because the second instance of polymer should be plural.

Claim 48 has been amended so that the second instance of polymer is now plural.

In view of the above, it is respectfully requested that these claim objections be withdrawn.

The rejections under 35 U.S.C. §112

Claims 1-64 were rejected for lack of enablement because, according to the Office Action (page 3): "[T]he specification, while being enabling for methods and carriers for transporting polyanionic macromolecules across a cellular membrane, does not reasonably provide enablement for methods and carriers for transporting polyanionic macromolecules across cellular biological barriers other than membranes, as broadly claimed." The Office Action (page 5) stated that: "This rejection can be overcome by substituting 'membrane' for 'biological barrier' in the claims."

The Applicant does not agree with this rejection and reserves the right to contest it in continuing applications. Nevertheless, in the interest expediting the issuance of allowable subject matter in the present application, the claims have been amended according to the suggestion in the Office Action. Therefore, it is respectfully requested that this rejection be withdrawn.

Claims 8, 12-16, 20, 21, 38-40, 57-59, and 61 were rejected as being indefinite.

Claim 8 was rejected as being indefinite because it lacked a period.

Claim 8 has been amended to add a period.

Claims 12-16, 20, 21, 38-40, 57-59, and 61 were rejected as being indefinite because of a lack of recitation of units of weight or mass.

Claims 12-16, 20, 21, 38-40, 57-59, and 61 have been amended to make explicit that the molecular weight unit is daltons.

In view of the above, it is respectfully requested that these rejections be withdrawn.

<u>The rejection under 35 U.S.C. §102(a)</u>

Claims 1-7, 9-15, 17, 20, 22-25, 27, 30-39, 41-44, 48-51, 53-58, 60, and 61 were rejected as being anticipated by WO 98/19710 (Schacht).

The Applicant respectfully traverses this rejection. Applicant claims a carrier in which the backbone molecule is a biocompatible hydrophilic polymer and polycationic molecules are linked to the backbone. This structure is illustrated in Fig. 1 of the present application, showing the backbone as a single hydrophilic molecule to which the polycationic polymer is appended. Although not shown in Fig. 1, in Applicant's invention multiple polycationic polymers are appended to the single hydrophilic backbone polymer molecule. See, *e.g.*, page 4, line 26-page 5, line 2:

> <u>Two or more</u> polycationic polymer fragments are covalently linked to <u>a</u> biocompatible hydrophilic backbone polymer by linkers. (emphasis added)

It is therefore clear to one skilled in the art from the specification that the term "backbone" refers to the single anchoring biocompatible hydrophilic molecule to which the multiple polycationic polymer molecules are linked. In contrast, Schacht does not disclose a carrier in which the backbone molecule is a biocompatible hydrophilic polymer. As shown in Fig. 3 of the reference, in Schacht's carriers the polycationic polymer molecule serves as the backbone to which multiple hydrophilic polymers (pHPMA) are appended. This configuration is the opposite of Applicant's carriers, and Schacht does not teach or suggest employing the hydrophilic polymer as the backbone molecule as presently claimed.

It is not surprising that Schacht's carriers and complexes are structurally different from those of the present invention, since Schact teaches a very different method of making carriers and complexes than does the present invention. The carriers of Schacht are made by first complexing DNA to the polycationic polymer and then adding a shell of hydrophilic polymer to the already-complexed DNA/polycationic polymer. See, *e.g.*, page 19, lines 10-11: "Self-assembly of poly(L-lysine) with DNA and bioactive oligopeptides prior to coating with reactive hydrophilic polymers." See also page 23, lines 9-11: "Poly(L-lysine)/DNA complexes were prepared at a charge ratio of 4, with or without the addition of IN177-SGSC, and were coated with a reactive hydrophilic polymer as described above." See also page 25, lines 25-26: "Formation of a complex of DNA with a partially modified polyamine followed by grafting of polyethylene glycol via a disulfide bond." See also page 35, lines 14-29:

> As described in Example 7, after self-assembly with DNA the cationic polymers may be linked to one or more hydrophilic polymers to form in effect graft block copolymers, this being achieved by providing reactive groups spaced along the length of the cationic polymers. In some embodiments, the preferred reactive groups for bringing about this coupling, either at the ends or on side chains along the main polymer backbone, are conveniently provided by reactive amine or thiol groups. The present example, shown in the diagram of FIGURE 3 of the accompanying drawings, describes the preparation of graft copolymers by the reaction of poly(HPMA)-COOH with cationic polymers bearing primary amino groups in their side chains [poly(Lys), poly(Ma-Gly-NH-(CH2)-NH2, poly(Ma-NH-(CH2)-NH2, etc.].
>
> In practice, this reaction would be carried out after self-assembly of the cationic polymer with nucleic acid to form the initial cationic polymer nucleic acid polyelectrolyte complex, but for the sake of simplicity a typical procedure followed for the synthesis of such graft block copolymers which may be represented as polycation-gr-poly(HPMA) is described omitting the first step of assembling the nucleic acid complex.

In view of the above described clear structural differences between the carriers and complexes of Schacht and those of the present invention, it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §103(a)

Claims 1, 17, 18, 19, 28, 29, 31, 46, 47, 48, 63, and 64 were rejected as being obvious over Schacht.

The Applicant respectfully traverses this rejection. Schacht teaches that it is important to first form a complex of the polycationic polymer and the polyanionic macromolecule before adding the hydrophilic polymer. See page 4, lines 27-31:

> Nucleic acid carrier vehicles as referred to above in accordance with the invention may be constructed by means of a stepwise process in which the cationic polymer is first self-assembled with the nucleic acid material to

> form a complex that provides a core portion of the complete carrier vehicle, and the hydrophilic polymer material is then assembled in a subsequent step.

By following the above teaching of Schacht, one would be led away from the present invention. The two-step procedure of Schacht initially results in a plurality of polycationic polymer molecules associated with the nucleic acid in a cationic polymer core, as described at page 4, lines 10-11 ("The cationic polymer core, which is generally made up of a plurality of polycation molecules..."). Each polycationic polymer molecule in the cationic polymer core has multiple reactive sites available for linking to the hydrophilic polymer, as described at page 3, lines. 13-20:

> This self-assembly with the nucleioc acid involves an association or binding between molecules of the polycationic component and theh polyanionic nucleic acid component. In the complex so formed, the nucleic acid is condensed in the core portion and at leas tsome of the said reactive groups on the molecules of the cationic polymer component are presented at the surface thereof. These reactive groups can then be coupled or linked with hydrophilic polymer molecules......

Therefore, in Schacht each polycation molecule serves as the "backbone" to which multiple hydrophilic polymer molecules may be attached in the second step of the process for producing the carrier.

In contrast, Applicant's carriers are produced by linking a hydrophilic polymer molecule with multiple reactive sites to two or more polycationic polymer molecules, prior to forming any complex with the polyanion. See, *e.g.*, page 17, line 17- by way of example:

> The PEG has a number "m" of pendant propionic acid groups (PA) randomly grafted onto its backbone. PEG-mPA and anhydrous dichloromethane are combined with the protection of argon. Then p-nitrophenol and 4-dimethylaminopyridine (DMAP) are added to the solution. Then 1-[3-

> dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (EDC) is added to form a clear solution. Then acetic acid is added to the clear mixture. The clear reaction mixture is then mixed with a solution of polyethylenimine (PEI) in anhydrous dimethylformamide (DMF) under the protection of argon. The mixture may be concentrated on a rotary evaporator to remove most of the DMF solvent. The resulting product can be purified and concentrated to produce a wax product. The crude wax product can be further purified on a gel filtration column to yield purified PEG-mPA-PEI.

After the hydrophilic and polycationic polymers are linked as described above and the carrier is formed, it is complexed with the polyanion as illustrated in Example 12, pg. 26, lns. 4-12 ("A solution of the carrier copolymer was created.....The solution was then mixed with about 2.0 μL of 0.1 mM oligonucleotide solution..."

This process is substantially different from that taught by Schacht and results in a carrier in which the hydrophilic polymer serves as the "backbone" instead of the polycationic polymer. Schacht provides no motivation to make a carrier with a hydrophilic backbone, as opposed to a polycationic polymer backbone, and provides no method for successfully making a carrier with a hydrophilic backbone.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 1, 7, 8, 17, 25, 26, 31, 45, 48, and 52 were rejected as being obvious over Schacht in view of U.S. Patent No. 5,777,078 (Bayley).

As explained above, the present claims are non-obvious over Schacht because Schacht neither teaches carriers with a hydrophilic polymer backbone nor provides a

process capable of making such carriers. Bayley was cited for the proposition that the use of lytic agents in carriers was known. This disclosure of Bayley, even if true, cannot remedy the deficiencies of Schacht. Therefore, the combination of Schacht and Bayley cannot make obvious the present claims.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 1, 16, 17, 21, 31, 38-40, 48, 57, 59, 60, and 62 were rejected as being obvious over Schacht in view of U.S. Patent Application Publication No. 2001/0005717 (Wagner).

As explained above, the present claims are non-obvious over Schacht because Schacht neither teaches carriers with a hydrophilic polymer backbone nor provides a process capable of making such carriers. Wagner was cited for the proposition that the use of PEI having certain molecular weight ranges in carriers was known. This disclosure of Wagner, even if true, cannot remedy the deficiencies of Schacht. Therefore, the combination of Schacht and Wagner cannot make obvious the present claims.

The Applicant wishes to point out that, like Schacht, Wagner differs from the present claims in that Wagner is directed to hydrophilic polymers linked to backbones of polycationic polymers while the present claims are directed to polycationic polymers linked to backbones of hydrophilic polymers. Wagner teaches away from the use of

hydrophilic polymers as backbones because Wagner teaches that it is important that the hydrophilic polymers be mobile. See paragraph [0023]:

> The hydrophilic polymer bound to PEI is preferably linear or branched only to a small extent, so that its mobility is largely maintained. (Without wishing to be tied to this theory, the beneficial effects of the polymer, besides its hydrophilicity, would appear to be attributable to its mobility.)

If the hydrophilic polymer serves as a backbone, and polycationic polymers are linked to that backbone as presently claimed, the mobility of the hydrophilic polymer would be expected to decrease since the hydrophilic polymer would have branchpoints along its length, formed by the linked polycationic polymers. Wagner explicitly discourages branchpoints in the hydrophilic polymer. Thus, Wagner teaches against modifying the disclosure of Wagner or the disclosure of Schacht (which also employs the polycationic polymer as the backbone) to arrive at the present invention.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 31, 32, and 37 were rejected as being obvious over Schacht in view of U.S. Patent No. 5,681,747 (Boggs).

As explained above, the present claims are non-obvious over Schacht because Schacht neither teaches carriers with a hydrophilic polymer backbone nor provides a process capable of making such carriers. Boggs was cited for the proposition that the use of certain types of oligonucleotides was known. This disclosure of Boggs, even if true,

cannot remedy the deficiencies of Schacht. Therefore, the combination of Schacht and Boggs cannot make obvious the present claims.

In view of the above, it is respectfully requested that this rejection be withdrawn.

In view of the foregoing remarks, the Applicant respectfully submits that all of the pending claims of the subject application are in condition for allowance. Prompt reconsideration and allowance of the present application is therefore earnestly solicited.

The time for responding to the Office Action was set for May 17, 2004. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response.

The Applicant hereby also makes a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon &

Kenyon's Deposit Account No. 11-0600 for any fees associated with such Conditional Petition.

Respectfully submitted,

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